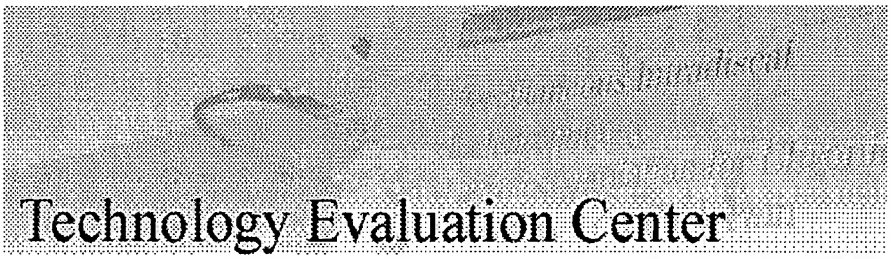
This is Google's cache of http://www.bcbs.com/tec/vol17/17_22.html as retrieved on Aug 1, 2006 12:27:36 GMT.
Google's cache is the snapshot that we took of the page as we crawled the web.
The page may have changed since that time. Click here for the current page without highlighting.
This cached page may reference images which are no longer available. Click here for the cached text only.
To link to or bookmark this page, use the following url: http://www.google.com/search?q=cache:qkKyU1R-eT4J:www.bcbs.com/tec/vol17/17_22.html+restenosis+ineffective&hl=en&gl=us&ct=clnk&cd=20

Google is neither affiliated with the authors of this page nor responsible for its content.

These search terms have been highlighted: **restenosis ineffective**



TEC Home
What Is TEC?
Kaiser Collaboration
Evidence-Based Medicine
AHRQ EPC
TEC Assessments
TEC Criteria
Medical Advisory Panel
Contact Us

TEC Search: Go

TEC Assessment Index

Email this page

Brachytherapy for the Prevention of Restenosis in Peripheral Arteries Following PTA of the Femoropopliteal System

Assessment Program
Volume 17, No. 22
February 2003

Executive Summary

Peripheral arterial disease (PAD) of the femoropopliteal system is a major cause of morbidity and limb loss. Medical therapy is often **ineffective** in controlling symptoms and preventing disease progression. Surgical bypass is an effective treatment for patients who fail medical therapy or who have limb-threatening ischemia. However, open surgery has substantial risks, especially for patients with co-existing cardiopulmonary disorders. Percutaneous transluminal angioplasty (PTA) is a lessinvasive alternative to open surgery and has been utilized for several decades in the femoropopliteal system. The main limitation of femoropopliteal PTA is "late" **restenosis** (within 6 months of the procedure), which occurs at rates even higher than with coronary PTA (PTCA), or with PTA of other peripheral vascular systems such as the aortoiliac. In addition, this high **restenosis** rate has not been reduced by the use of adjunctive agents such as stents.

Peripheral artery brachytherapy, the delivery of radiation to peripheral arteries through local catheters, is intended to reduce **restenosis** following PTA. This Assessment examines whether peripheral artery brachytherapy improves outcomes when used as an adjunct to PTA in the femoropopliteal system. Brachytherapy may reduce the rate of late **restenosis** following PTA and therefore reduce the need for further revascularization procedures, especially open surgery. It may also improve outcomes of PAD such as symptoms, exercise tolerance, and reduce the need for amputation.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether peripheral artery brachytherapy as an adjunct to percutaneous transluminal angioplasty (PTA) for the prevention of **restenosis** in the femoropopliteal system meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

There are currently three intravascular brachytherapy devices that have U.S. Food and Drug Administration (FDA) approval for use in the coronary system. The Novoste Beta-Cath™ system and the Guidant Galileo® system are beta-radiation catheters, while the Cordis Checkmate™ system is a gamma-radiation catheter. There are currently no brachytherapy devices approved specifically for use in the peripheral arterial system.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

The scientific evidence consists of two randomized trials comparing PTA plus brachytherapy with PTA alone. The first trial of 117 patients (Vienna-2) was unblinded and had broad eligibility criteria, enrolling many patients with high-risk lesions that would not typically be treated with PTA. This trial showed a significantly lower rate of angiographic **restenosis** at 6 months in favor of the brachytherapy group (28.3 vs. 53.7%, $p<0.05$). On subgroup analysis, there was variability in treatment effect, with a greater magnitude of benefit seen for higher risk lesions.

The second trial was smaller, reporting on 22 evaluable patients. This trial was single-blinded with a sham placebo control, and included patients with lower-risk lesions, more closely reflecting clinical indications for PTA. Relevant 6-month outcomes in this trial were **restenosis** rates and exercise tolerance. Angiographic **restenosis** at 6 months was seen in 5 of 12 patients in the PTA-alone group and 0 of 12 patients in the brachytherapy group (p=NS). Exercise tolerance, measured by total walking distance and pain-free walking distance, was not significantly different between groups.

In summary, both of these trials have limitations that preclude conclusions on whether brachytherapy is efficacious for the population under consideration. The Vienna-2 trial was unblinded and had no placebo control. It also enrolled heterogeneous subgroups of patients, many who would not be clinically eligible for PTA. The benefit of PTA varied according to the subgroups examined, making it difficult to determine which patients actually benefit from the procedure. The second trial was single-blinded with a sham brachytherapy placebo control. However,
this trial only reported on 22 patients and used an unusual outcome measure (mean change in vessel stenosis) as primary outcome. Reported outcomes from this trial that were relevant to this review, i.e., 6-month **restenosis** rate and exercise tolerance, were not significantly different between groups.

A number of ongoing randomized controlled trials of peripheral artery brachytherapy should report results within the next 1–2 years. These trials will add significant data to these currently available and allow a fuller evaluation of whether brachytherapy is an effective adjunct to PTA in the femoropopliteal system.

3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives.

The evidence does not permit conclusions on whether peripheral artery brachytherapy as an adjunct to PTA for the prevention of **restenosis** in the femoropopliteal system improves health outcomes or is as beneficial as any established alternatives.

5. The improvement must be attainable outside the investigational settings.

Whether peripheral artery brachytherapy as an adjunct to PTA for the prevention of **restenosis** in the femoropopliteal system improves health outcomes has not been demonstrated in the investigational setting.

Based on the above, peripheral artery brachytherapy as an adjunct to PTA for the prevention of **restenosis** in the femoropopliteal system does not meet the TEC criteria.

Full Study

Brachytherapy for the Prevention of Restenosis in Peripheral Arteries Following PTA of the Femoropopliteal System

Full studies are in PDF format. You will need Adobe Acrobat Reader to view all studies.

Download Adobe Acrobat Reader here.

TEC Assessment Index

NOTICE OF PURPOSE: TEC Assessments are scientific opinions, provided solely for informational purposes. TEC Assessments should not be construed to suggest that the Blue Cross Blue Shield Association, Kaiser Permanente Medical Care Program or the TEC Program recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service; any particular course of treatment, procedure, or service; or the payment or non-payment of the technology or technologies evaluated.

KEYWORDS: CardiovascularMedicine (category); Surgery/Surgical Alternatives/Interventional Radiology (category); angiographic restenosis; angiography; angioplasty; antiplatelet therapy; balloon angioplasty; Beta-Cath; beta radiation; beta-radiation catheter; brachytherapy; bypass grafting; CAD; circulation; Checkmate; claudication; coronary artery disease; endovascular brachytherapy; femoral artery; femoropopliteal bypass; femoropopliteal system; Galileo; gamma radiation; gamma-radiation catheter; ischemia; lipid-lowering therapy; PAD; peripheral artery; peripheral artery brachytherapy; peripheral arterial disease; peripheral arterial occlusive disease; peripheral circulation; peripheral vascular disease; percutaneous transluminal angioplasty; PTA; radiation; radioactive particles; radiotherapy; restenosis; revascularization; surgical bypass; surgery; therapy; treatment; vascular brachytherapy; vascular surgery; Vienna-2 trial peripheral arterial disease

Copyright ©2006 Blue Cross Blue Shield Association.
An Association of Independent Blue Cross Blue Shield Plans. All rights reserved.

This is **G o o g l e**'s cache of http://www.genome.jp/dbget-bin/www_bget?omim+142360 as retrieved on Aug 19, 2006 11:28:47 GMT.
G o o g l e's cache is the snapshot that we took of the page as we crawled the web.
The page may have changed since that time. Click here for the current page without highlighting.
This cached page may reference images which are no longer available. Click here for the cached text only.
To link to or bookmark this page, use the following url: http://www.google.com/search?q=cache:ZIGgCqIwktcJ:www.genome.jp/dbget-bin/www_bget%3Fomim%2B142360+restenosis+ineffective&hl=en&gl=us&ct=clnk&cd=22

Google is neither affiliated with the authors of this page nor responsible for its content.

These search terms have been highlighted: **restenosis ineffective**

Database: OMIM
Entry: 142360

MIM Entry: 142360
Title:
+142360 HEPARIN COFACTOR II; HCF2
;;LEUSERPIN 2; LS2;;
SERPIND1
HCF II DEFICIENCY, INCLUDED;;
THROMBOPHILIA DUE TO HEPARIN COFACTOR II DEFICIENCY, INCLUDED
Text:
The anticoagulant action of heparin is dependent on plasma components termed heparin cofactors. The first of these to be well characterized was antithrombin III (107300). Heparin cofactor II is antigenically distinct from AT III. HCF II is normal in patients with AT III deficiency and is low in patients with disseminated intravascular coagulation. Congenital deficiency of HCF II is inherited in an autosomal dominant fashion and is classified into type I (quantitative) and type II (qualitative) deficiency.

In a 42-year-old woman with intracranial thrombosis, Tran et al. (1985) found that HCF II was about 50% of normal. The same was true of the mother and sister, both of whom had had thrombotic complications. Sie et al. (1985) studied the family of a 36-year-old man with recurrent deep vein thrombosis and HCF II deficiency. The mother, half brother, and daughter likewise had low levels and some had an unusual frequency of thrombosis. Matsuo et al. (1992) reported a Japanese family with type I hereditary HCF II deficiency. The propositus, a 61-year-old man, had coronary artery disease requiring percutaneous transluminal coronary angioplasty 4 times in 1 year because of **restenosis**. Heparin was apparently **ineffective** in preventing **restenosis** by thrombin generation. After the fourth angioplasty, a specific thrombin inhibitor was used with success.

From a human liver cDNA library, Ragg (1986) isolated a new member of the protease inhibitor family. The inhibitor, named leuserpin 2, has 48 amino acids and contains a leucine residue at its putative reactive center. It shows about 25% to 28% homology to 3 human members of the plasma protease inhibitor family: antithrombin III, alpha-1-antitrypsin, and alpha-1-antichymotrypsin. Comparison with published partial amino acid sequences suggested that LS2 is closely related or identical to the thrombin inhibitor heparin cofactor II.

Using crossed immunolectrophoresis, Andersson et al. (1987) were the first to demonstrate molecular heterogeneity of the HCF II molecule, the so-called 'Oslo variant,' in affected members of 2 Norwegian families with HCF II deficiency. Their findings were consistent with an autosomal dominant pattern of inheritance; affected individuals had half the normal amount of normal HCF II and were presumed heterozygotes.

Blinder et al. (1988) isolated an apparently full-length cDNA for HCF II from a human liver cDNA library. Blot hybridization of a probe to DNA isolated from sorted human chromosomes indicated that the HCF2 gene is located on chromosome 22. Herzog et al. (1991) presented the complete nucleotide sequence of the HCF2 gene, which has 5 exons and 4 introns. By use of rodent-human somatic cell hybrids carrying only parts of human chromosome 22 and by study of a chronic myelogenous leukemia cell line, they localized the gene to 22q11, proximal to the breakpoint cluster region (151410).

Villa et al. (1999) reported a 29-year-old woman who at the age of 22 suffered a first episode of deep venous thrombosis in the lower right leg complicated by a pulmonary embolism 1 week after starting oral contraceptives. She was found to have type I deficiency of antithrombin III in heterozygous state and to be homozygous for HCF II deficiency. Her sister was also homozygous for HCF II deficiency but had normal levels of antithrombin III and had not suffered thrombotic events despite thrombotic risk factors such as the use of oral contraceptives, pregnancy, and surgery. Several other members of the family were heterozygous for HCF II deficiency but had not had thrombotic episodes despite circumstantial risk factors. This suggested that the thrombotic risk in an individual with HCF II deficiency and normal AT levels is low.

In COS-1 cells transfected with the Tokushima variant of HCF II (P443L; 142360.0004), Kanagawa et al. (2001) observed immunohistochemical staining primarily in the perinuclear area. They concluded that impaired secretion of mutant HCF II molecules due to intracellular degradation is the molecular pathogenesis of type I congenital HCF II deficiency caused by this mutation.

Aihara et al. (2004) measured plasma HCF II activity, HDL cholesterol level, and carotid artery plaque thickness in 306 Japanese individuals over 40 (mean age, 68.9 years) and observed that HCF II activity decreased with age. Multiple regression analysis revealed that plasma HCF II activity and HDL cholesterol level were independently associated with decreased plaque thickness and that the antiatherogenic contribution of HCF II activity was stronger than that of HDL cholesterol.

Allelic Variants:

.0001
HEPARIN COFACTOR II DEFICIENCY
HCF2, ARG189HIS

By means of the polymerase chain reaction (PCR), Blinder et al. (1989) amplified DNA fragments encoding the N-terminal 220 amino acid residues of heparin cofactor II from a patient with the Oslo variant. A point mutation (G-to-A) resulting in substitution of his for arg189 was found in 1 allele. The same mutation was created in the cDNA of native heparin cofactor II by oligonucleotide-directed mutagenesis and was expressed in E. coli. The recombinant cofactor reacted with thrombin in the presence of heparin, but not dermatan sulfate, confirming that this mutation is responsible for the functional abnormality in HCF II Oslo.

.0002
HEPARIN COFACTOR II DEFICIENCY
HCF2, 1-BP INS

Kondo et al. (1996) studied the defect in a Japanese patient with type I HCF II deficiency who suffered from angina pectoris and coronary artery disease. PCR-based sequence analysis showed that the patient's HCF2 gene had a 1-bp insertion, a T after the GAT codon for asp88 in exon 2, resulting in a frameshift. The abnormal HCF II Awaji protein was predicted to have an altered amino acid sequence from position 89 and to terminate at residue 107, thus being composed of the NH2-terminal one-fifth of normal HCF II and therefore dysfunctional for thrombin

inhibition. The sister appeared to have the same mutation. Cellular studies suggested that the abnormal HCF II Awaji protein is secreted normally but rapidly degraded in the circulating blood.

.0003
HEPARIN COFACTOR II DEFICIENCY
HCF2, 2-BP DEL, 12896TT

In 2 unrelated patients from the Rimini province in northern Italy with type I HCF II deficiency and thrombophilia (188050), Bernardi et al. (1996) identified heterozygosity for a 2-bp deletion (12896delTT) in exon 5 of the HCF2 gene, resulting in a frameshift at leu457 that elongates the protein by 4 amino acids. The variant was designated HCF II Rimini. In both probands, another hereditary thrombophilic alteration was diagnosed: the factor V Leiden mutation (R506Q; 227400.0001) was detected in 1 and type I protein C deficiency (see 176860) in the other. The tracing of the single defects in several unaffected members of each family indicated that the mutations clinically manifested only in the doubly heterozygous condition; the asymptomatic son of the proband with the HCF2 deletion and the factor V Leiden mutation was the only other double heterozygote detected.

.0004
HEPARIN COFACTOR II DEFICIENCY
HCF2, PRO443LEU

In a 66-year-old Japanese woman with type I congenital HCF II deficiency and widespread atherosclerotic lesions, Kanagawa et al. (2001) identified a heterozygous 12854C-T transition in exon 5 of the HCF2 gene, resulting in a pro443-to-leu (P443L) substitution. The variant, which was designated HCF II Tokushima, was found in 6 other family members with HCF II deficiency, but not in healthy unaffected individuals. Transfected COS-1 cells exhibited perinuclear immunohistochemical staining, indicating impaired secretion of the mutant HCF II molecules due to intracellular degradation.

References:

1. Aihara, K.; Azuma, H.; Takamori, N.; Kanagawa, Y.; Akaike, M.; Fujimura, M.; Yoshida, T.; Hashizume, S.; Kato, M.; Yamaguchi, H.; Kato, S.; Ikeda, Y.; Arase, T.; Kondo, A.; Matsumoto, T.: Heparin cofactor II is a novel protective factor against carotid atherosclerosis in elderly individuals. Circulation 109: 2761-2765, 2004.

2. Andersson, T. R.; Larsen, M. L.; Abildgaard, U.: Low heparin cofactor II associated with abnormal crossed immunoelectrophoresis pattern in two Norwegian families. Thromb. Res. 47: 243-248, 1987.

3. Bernardi, F.; Legnani, C.; Micheletti, F.; Lunghi, B.; Ferraresi, P.; Palareti, G.; Biagi, R.; Marchetti, G.: A heparin cofactor II mutation (HCII Rimini) combined with factor V Leiden or type I protein C deficiency in two unrelated thrombophilic subjects. Thromb. Haemost. 76: 505-509, 1996.

4. Blinder, M. A.; Andersson, T. R.; Abildgaard, U.; Tollefsen, D. M.: Heparin cofactor II(Oslo): mutation of arg-189-to-his decreases the affinity for dermatan sulfate. J. Biol. Chem. 264: 5128-5133, 1989.

5. Blinder, M. A.; Marasa, J. C.; Reynolds, C. H.; Deaven, L. L.; Tollefsen, D. M.: Heparin cofactor II: cDNA sequence, chromosome localization, restriction fragment length polymorphism, and expression in Escherichia coli. Biochemistry 27: 752-759, 1988.

6. Herzog, R.; Lutz, S.; Blin, N.; Marasa, J. C.; Blinder, M. A.; Tollefsen, D. M.: Complete nucleotide sequence of the gene for human heparin cofactor II and mapping to chromosomal band 22q11. Biochemistry 30: 1350-1357, 1991.

7. Kanagawa, Y.; Shigekiyo, T.; Aihara, K.; Akaike, M.; Azuma, H.; Matsumoto, T.: Molecular mechanism of type I congenital heparin cofactor (HC) II deficiency caused by a missense mutation at reactive P2 site: HC II Tokushima. Thromb. Haemost. 85: 101-107, 2001.

8. Kondo, S.; Tokunaga, F.; Kario, K.; Matsuo, T.; Koide, T.: Molecular and cellular basis for type I heparin cofactor II deficiency (heparin cofactor II Awaji). Blood 87: 1006-1012, 1996.

9. Matsuo, T.; Kario, K.; Sakamoto, S.; Yamada, T.; Miki, T.; Hirase, T.; Kobayashi, H.: Hereditary heparin cofactor II deficiency and coronary artery disease. Thromb. Res. 65: 495-505, 1992.

10. Ragg, H.: A new member of the plasma protease inhibitor gene family. Nucleic Acids Res. 14: 1073-1088, 1986.

11. Sie, P.; Dupouy, D.; Pichon, J.; Boneu, B.: Constitutional heparin co-factor II deficiency associated with recurrent thrombosis. Lancet II: 414-416, 1985.

12. Tran, T. H.; Marbet, G. A.; Duckert, F.: Association of hereditary heparin co-factor II deficiency with thrombosis. Lancet II: 413-414, 1985.

13. Villa, P.; Aznar, J.; Vaya, A.; Espana, F.; Ferrando, F.; Mira, Y.; Estelles, A.: Hereditary homozygous heparin cofactor II deficiency and the risk of developing venous thrombosis. Thromb. Haemost. 82: 1011-1014, 1999.

Clinical Synopsis:

Heme:
Disseminated intravascular coagulation;
Intracranial thrombosis;
Recurrent deep vein thrombosis

Cardiac:
Post-angioplasty coronary artery **restenosis**

Lab:
Heparin cofactor II deficiency

Inheritance:
Autosomal dominant (22q11)

Contributors:
Marla J. F. O'Neill - updated: 1/31/2006
Marla J. F. O'Neill - updated: 5/16/2005
Victor A. McKusick - updated: 12/13/1999
Alan F. Scott - edited: 12/27/1996

Creation Date:
Victor A. McKusick: 6/4/1986

Edit Dates:
wwang: 02/03/2006
terry: 1/31/2006
wwang: 7/11/2005
wwang: 7/7/2005
terry: 5/16/2005
terry: 6/2/2004
joanna: 3/17/2004
terry: 3/13/2002
mcapotos: 12/17/1999
mcapotos: 12/16/1999
terry: 12/13/1999
mark: 12/27/1996
mark: 3/21/1996

```
  terry: 3/13/1996
  mimadm: 9/24/1994
  carol: 10/9/1992
  supermim: 3/16/1992
  carol: 8/7/1991
  supermim: 3/20/1990
  ddp: 10/27/1989

OMIM
```

DBGET integrated database retrieval system, GenomeNet